#9

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re: U.S. Patent No. 4,282,251 :

Issued: August 4, 1981 :

To: Daniel Berney :

For: TRANS-N-CINNAMYL-N-METHYL-(1-NAPHTHYLMETHYL)AMINE :

I hereby certify that this correspondence is being deposited with the United States Postal Service as first class mail in an envelope addressed to: Commissioner of Patents and Trademarks, Washington, D.C. 20231, on April 25, 1988
(Date of Deposit)
Robert S. Honor
Name of applicant, assignee, or Registered Representative
Robert S Honor
Signature
April 25, 1988
Date of Signature

Honorable Commissioner of
Patents and Trademarks
Washington, D.C. 20231

Dear Sir:

This concerns an Application for Patent Extension under 35 USC 156 regarding the above-identified U.S. patent which is attached hereto in duplicate.

Enclosed is a return postcard.

The Commissioner is hereby authorized to charge to Deposit Account No. 19-0134 any amount due in connection with the filing fee of said Application for Patent Extension.

A duplicate of this sheet is appended.

Respectfully submitted,

Robert S Honor

Robert S. Honor
Attorney for Applicant
(201) 503-8474

SANDOZ CORPORATION
59 Route 10
E. Hanover, NJ 07936

RSH/vls

Date: April 25, 1988

Enclosures: Application for Patent Extension (in duplicate)
Return Postcard
Dupl. Copy Deposit Account Charge Authorization

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

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APPLICATION FOR PATENT TERM EXTENSION
UNDER 35 USC 156

Honorable Commissioner of
Patents and Trademarks
Washington, D.C. 20231

Sir:

I. Applicant, Sandoz Pharmaceuticals Corporation, a corporation of the State of Delaware, represents that it is the assignee of the entire interest in and to Letters Patent of the United States No. 4,282,251 identified above by virtue of assignments in favor of:

1. Sandoz Ltd. from and by Daniel Berney, recorded at the U.S. Patent Office on March 2, 1981 at Reel 3834, Frame 009, and
2. Fidelity Union Trust Company from and by Sandoz Ltd., recorded at the U.S. Patent and Trademark Office on October 18, 1982 at Reel 4055, Frame 0740, and
3. Sandoz, Inc. from and by Fidelity Union Bank, recorded at the U.S. Patent and Trademark Office on September 26, 1983 at Reel 4172, Frame 0924. The name Sandoz, Inc. was changed to Sandoz Pharmaceuticals Corporation as of October 16, 1985 at Reel 0507, Frame 0956 and notice of indexing of this name change respecting U.S. Patent 4,282,251 was communicated in writing to the U.S. Patent and

Trademark Office by Deposit Account Order Form dated April 12, 1988, Deposit Account No. 19-0134. The name Fidelity Union Trust Company was changed to Fidelity Union Bank at Reel 4507, Frame 0368.

II. Applicant submits this Application for Extension of Patent Term under 35 USC 156 by providing the following information as required by 37 CFR §1.710 through §1.785, especially §1.740.

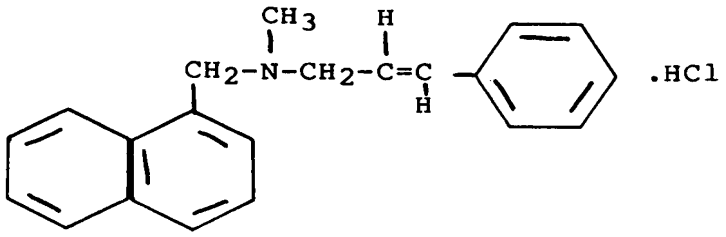
1. The complete identification of the approved product is

chemical name: Trans-N-(cinnamyl)-N-methyl-(1-naphthylmethyl)amine hydrochloride,

also known as (E)-N-cinnamyl-N-methyl-1-naphthalenemethylamine hydrochloride

generic name: naftifine hydrocholoride

chemical structure:



2. Regulatory Review has taken place under the Federal Food, Drug and Cosmetic Act (21 U.S. Code 355) Section 505(b).

3. The product received permission for commercial marketing or use under the Federal Food, Drug and Cosmetic Act Section 505(b) on February 29, 1988.

4. The sole active ingredient in the product is naftifine hydrochloride, and naftifine hydrochloride (or

naftifine or any other salt thereof) has not been previously approved for commercial marketing or use under the Federal Food, Drug and Cosmetic Act.

5. This application is being submitted within the sixty (60) day period permitted for submission pursuant to 37 CFR §1.720(f). The last day on which this application could be submitted is April 28, 1988.

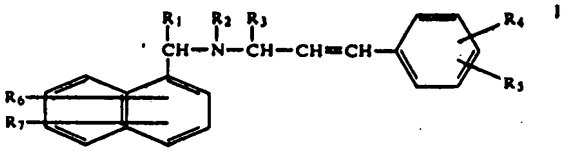
6. The U.S. patent for which an extension is being sought is U.S. 4,282,251, patented by Daniel Berney on August 4, 1981, and expiring normally on August 4, 1998.

7. A copy of U.S. patent 4,282,251 is attached hereto as Appendix A.

8. No disclaimer, certificate of correction, receipt of maintenance fee payment or re-examination certificate has been issued or is of relevance in connection with U.S. Patent 4,282,251.

9. U.S. Patent 4,282,251 claims the product naftifine hydrochloride, a composition containing same, or its relevant use in each of claims 1, 2, 3, 4, 5, 6, 28 and 29.

i) **1. Compounds of formula I,**



I

in which
R_1 is hydrogen or alkyl,
R_2 is alkyl, alkenyl, alkynyl, cycloalkyl or cycloalkylalkyl,
R_3 is hydrogen or lower alkyl, and
R_4, R_5, R_6 and R_7, which may be the same or different, each signifies hydrogen, halogen, trifluoromethyl, hydroxy, nitro or lower alkyl or alkoxy, and
chemotherapeutically acceptable acid addition salts thereof.

When R_1 is hydrogen

R_2 is alkyl

R_3 is hydrogen, and

R_4, R_5, R_6 and R_7 are hydrogen,

and when the acid addition salt included in this claim 1 is the hydrochloride, naftifine hydrochloride is described and specifically defined.

ii) **2. A chemotherapeutic composition comprising a chemotherapeutic effect amount of a compound of claim 1 in association with a chemotherapeutically acceptable diluent or carrier.**

The chemotherapeutic composition embraces naftifine hydrochloride when all the substituents and the salt are as described as explained above for claim 1.

iii) **3. A method of treating mycotic disorders comprising administering to an animal in need of such treatment, an effective amount of a compound of claim 1.**

The method claimed requires use of an effective amount of a compound of claim 1. It concerns the treatment of mycotic disorders which is also the object of NDA 19-599 of relevance here.

iv) **4. A compound according to claim 1 in which R_2 is alkyl of 1 to 6 carbon atoms.**

This claim is dependent from claim 1 and additionally requires that the alkyl group of R_2 contain 1 to 6 carbon atoms which in turn permits the compound described to be within the scope of II.9.i) above.

v) **5. A compound according to claim 4 in which R_1 is hydrogen and R_3 is hydrogen.**

R_1 and R_3 of claim 4 (in turn dependent upon claim 1) are required to be hydrogen which permits the compound described to lie within the scope of II.9.i) above.

vi) **6. The compound of claim 1 which is Trans-N-(cinnamyl)-N-methyl-(1-naphthylmethyl)amine.**

The compound named in this claim corresponds to the free base of natifine hydrochloride as identified in II.1. above.

vii) **28. A pharmaceutical composition according to claim 2 in which the compound is Trans-N-cinnamyl-N-methyl(1-naphthylmethyl)amine.**

The pharmaceutical composition names the the free base of naftifine hydrochloride as identified in II.1. above.

viii) **29. A method according to claim 3 in which the compound is Trans-N-cinnamyl-N-methyl-(1-naphthylmethyl)amine.**

The method claimed specifically requires use of the free base of naftifine hydrochloride as identified in II.1. above.

10. The relevant effective date of an exemption under subsection (i) of Section 505 of the Federal Food Drug and Cosmetic Act (IND No. 17-148) is January 17, 1980. This IND was opened in the name of Dorsey Laboratories, then a division of Sandoz, Inc. Sandoz, Inc. assumed responsibility for the IND on July 22, 1983 and the IND was discontinued by Sandoz, Inc. on April 29, 1986 (acknowledged by the U.S. Food and Drug Administration on May 16, 1986). On August 5, 1983, the Food and Drug Administration was advised that Sandoz, Inc. was granting a cross reference right to said IND to Allergan Pharmaceuticals, Inc. (now formally Allergan, Inc. due to a change of name effective in September, 1986) and this was formalized between the parties by virtue of a license agreement dated October 10, 1983 granting to Allergan rights to develop and sell naftifine hydrochloride under Sandoz patents and know-how.

On October 7, 1983, Allergan Pharmaceuticals, Inc. through its division, Herbert Laboratories, mailed an original IND application to the Food and Drug Administration. That act was acknowledged by the Food and Drug Administration on October 18, 1983, indicating receipt of the IND (No. 22,919) on October 11,, 1983.

The relevant date a New Drug Application (NDA) was initially submitted under Section 505(b) (NDA No. 19-599) is March 14, 1986. The relevant date such application was approved under Section 505(b) is February 29, 1988. The above dates and information are to enable the Secretary of Health and Human Services to determine the applicable regulatory review period.

11. Attached is Appendix B containing a brief description of the activities undertaken by Sandoz, Inc., (now Sandoz Pharmaceuticals Corporation), owner of U.S. Patent 4,282,251, and Allergan, Inc., licensee of Sandoz, Inc. These activities took place during the applicable regulatory review period with respect to naftifine hydrochloride as indicated by the dates pertaining to such activities.

Respecting the regulatory history of IND 17-148 filed by the Dorsey division of Sandoz, Inc., (predecessor of Sandoz Pharmaceuticals Corporation), it should be noted that the studies reported by Sandoz to FDA on July 13, 1983 and the data and information contained in said early studies permitted Sandoz' licensee, Allergan Pharmaceuticals, Inc. to move with dispatch into the filing of its own IND (No. 22,919) and the additional clinical studies which resulted in the fiing of NDA 19-599 by Allergan.

A brief description of the relevant dates and activities is attached hereto as Appendix B hereof. Part 1 of said Appendix pertains to activities of Sandoz Pharmaceuticals Corporation or a predecessor company, whereas Part 2 of said Appendix B pertains to activities of Allergan, Inc.

12. In the opinion of Sandoz Pharmaceuticals Corporation, U.S. Patent 4,282,251 is eligible for the extension herein applied for because it satisfies all of the requirements for such extension as follows:

(i) 35 USC 156(a)

U.S. patent 4,282,251 claims a product and a method of using a product.

(ii) 35 USC 156(a)(1)

The term of U.S. patent 4,282,251 has not expired before submission of this application.

(iii) 35 USC 156(a)(2)

The term of U.S. Patent 4,282,251 has never been extended.

(iv) 35 USC 156(a)(3)

The application for extension is submitted by the owner of record.

(v) 35 USC 156(a)(4)

The product, naftifine hydrochloride, has been subject to a regulatory review period before its commercial marketing or use.

(vi) 35 USC 156(a)(5)(A)

The commercial marketing or use of the product, naftifine hydrochloride, after the regulatory review period indicated herein is the first permitted commercial marketing or use of the product under provisions of the Federal Food, Drug and Cosmetic Act (21 USC 355) under which such regulatory review occurred.

The length of the extension requested is two years, and was determined by the following calculation:

(A) i) Date of filing of Sandoz, Inc. IND - January 17, 1980

ii) Date of filing of Allergan Pharmaceuticals, Inc. IND - October 7, 1983

iii) Date of filing of Allergan Pharmaceuticals, Inc. NDA - March 14, 1986

iv) Date of Approval of Allergan, Inc. NDA - February 29, 1988

(B) Span under 35 USC 156(g)(1)(B)(i) between January 17, 1980 and March 14, 1986 equals 6 yrs., 1 month and 25 days.

(C) Span under 35 USC 156(g)(1)(B)(ii) between March 14, 1986 and February 29, 1988 equals 1 yr., 11 months and 15 days.

(D) Half of 6 yrs., 1 month, 25 days (from B) equals 3 yrs., 0 months, 28 days.

(E) Plus (from C) 1 yr., 11 months, 15 days

(F) Total 4 yrs, 11 months, 43 days

(G) Maximum extension allowable equals 2 yrs; 35 USC 156(g)(4)(C).

(H) The period remaining in the term of U.S. Patent 4,282,251 after NDA approval is 10 years, 6 months and 4 days which, when added to the 2 years requested by applicant, is less than 14 years and thus in compliance with 35 USC 156(c)(3).

13. Sandoz Pharmaceuticals Corporation acknowledges a duty to disclose to the Commissioner of Patents and Trademarks and the Secretary of Health and Human Services any information which is material to the determination of entitlement to the extension sought by this application.

14. A letter in duplicate authorizing the Commissioner of Patents to charge the required fee or fees for receiving and acting upon this APPLICATION FOR PATENT TERM EXTENSION UNDER 35 USC 156 to Deposit Account No. 19-0134 is being mailed on even date herewith.

15. All inquiries and correspondence relating to this application for patent term extension should be directed to:

Gerald D. Sharkin
Patent and Trademark Affairs
Sandoz Pharmaceuticals Corporation
59 Route 10
E. Hanover, New Jersey 07936

16. The undersigned hereby certifies that a duplicate original of this application for extension is submitted herewith.

17. Attached hereto as Appendix C hereof is a Declaration as set forth in paragraph (b) of 37 CFR §1.740.

It is respectfully requested that the above Extension of the Patent Term under 35 USC 156 of U.S. Patent No. 4,282,251 be granted.

Respectfully submitted,

By 

Robert S. Honor
Attorney for Applicant
Registration No. 22,801
(201) 503-8474

SANDOZ PHARMACEUTICALS CORPORATION
59 Route 10
E. Hanover, N.J. 07936

RSH/vls
Date: April 25, 1988

Enclosures: Appendices A, B and C

APPENDIX A

United States Patent [19]

Berney

[11] **4,282,251**

[45] **Aug. 4, 1981**

[54] **TRANS-N-CINNAMYL-N-METHYL-(1-NAPHTHYLMETHYL)AMINE**

[75] Inventor: **Daniel Berney**, Lausanne, Switzerland

[73] Assignee: **Sandoz Ltd.**, Basel, Switzerland

[21] Appl. No.: **100,024**

[22] Filed: **Dec. 3, 1979**

Related U.S. Application Data

[63] Continuation-in-part of Ser. No. 1,479, Jan. 8, 1979, abandoned, which is a continuation of Ser. No. 789,808, Apr. 22, 1977, abandoned.

[30] **Foreign Application Priority Data**

Apr. 28, 1976	[CH]	Switzerland	5335/76
Dec. 22, 1976	[CH]	Switzerland	16182/76
Jan. 26, 1977	[CH]	Switzerland	920/77
Jan. 26, 1977	[CH]	Switzerland	921/77

[51] **Int. Cl.**[3] **A01N 33/02**; A01N 37/30; C07C 87/28

[52] **U.S. Cl.** **424/316**; 260/501.1; 260/501.18; 260/501.19; 260/501.21; 424/330; 564/273; 564/274; 564/275; 564/363; 564/364; 564/365; 564/366; 564/383; 564/386; 564/387; 564/342; 564/343; 568/425; 568/426

[58] **Field of Search** ..... 260/570.8 R, 501.1, 260/501.18; 424/330, 316; 564/383, 387

[56] **References Cited**

U.S. PATENT DOCUMENTS

2,601,275	6/1952	Gump et al.	260/570.8 R
2,609,392	9/1952	Crossley	260/570.8 X
3,094,561	6/1963	Faust et al.	260/578.8 X
3,366,688	1/1968	Hargrove	260/594
3,829,469	8/1974	Thiele et al.	260/570.8 X

OTHER PUBLICATIONS

Biniecki et al. (I), "Chemical Abstracts", vol. 50, pp. 4096–4097 (1956).
Biniecki et al. (II), "Chemical Abstracts", vol. 49, p. 8153 (1955).
Gunn et al., "Chemical Abstracts", vol. 34, p. 8064.
Wagner et al., "Synthetic Organic Chemistry", pp. 666–669 (1953).

Primary Examiner—Robert V. Hines
Attorney, Agent, or Firm—Gerald D. Sharkin; Robert S. Honor; Thomas O. McGovern

[57] **ABSTRACT**

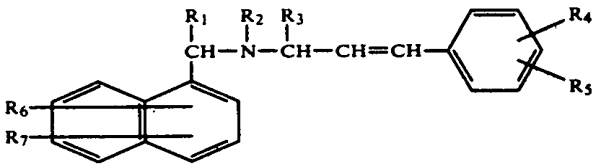
Cinnamylalkyl-1-naphthylmethylamines, useful as antimycotic agents, and processes for their production.

29 Claims, No Drawings

TRANS-N-CINNAMYL-N-METHYL-(1-NAPHTHYLMETHYL)AMINE

This application is a continuation-in-part of Ser. No. 01,479 filed Jan. 8, 1979 which in turn is a continuation of Ser. No. 789,808 filed Apr. 22, 1977, and now both abandoned.

This invention provides compounds of formula I,



I

in which

R_1 is hydrogen or alkyl,

R_2 is alkyl, alkenyl, alkynyl, cycloalkyl or cycloalkylalkyl,

R_3 is hydrogen or lower alkyl, and

R_4, R_5, R_6 and R_7, which may be the same or different, each signifies hydrogen, halogen, trifluoromethyl, hydroxy, nitro or lower alkyl or alkoxy.

It will be appreciated that the compounds of formula I exist in the form of cis and trans isomers. It is to be understood that the invention embraces both isomeric forms and mixtures thereof.

In the compounds of formula I, R_1 may be hydrogen. It may also be alkyl, which can be straight or branched chain, in particular of 1 to 6, preferably 1 to 4 carbon atoms, more particularly methyl.

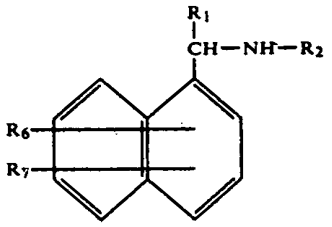
R_2 may be alkyl, which may be straight or branched chain, in particular of 1 to 6, preferably 1 to 4 carbon atoms, more particularly methyl. It may also be alkenyl, particularly of 3 to 6 carbon atoms, e.g. allyl. It may also be alkynyl of 3 to 6, preferably 3 or 4 carbon atoms. It may also be cycloalkyl, in particular of 3 to 6, preferably 5 or 6, ring carbon atoms. It may finally be cycloalkylalkyl. The cycloalkyl portion thereof suitably has 3 to 6, preferably 3 or 4, ring carbon atoms and the alkyl portion thereof suitably has 1 to 4, preferably 1 or 2, carbon atoms.

R_3 may be hydrogen. It may also be lower alkyl, preferably of 1 to 3 carbon atoms.

Any or all of R_4 to R_7 may signify (i) hydrogen; (ii) halogen; (iii) CF_3; (iv) OH; (v) NO_2; (vi) lower alkyl, preferably of 1 to 3 carbon atoms; or (vii) lower alkoxy, preferably of 1 to 3 carbon atoms.

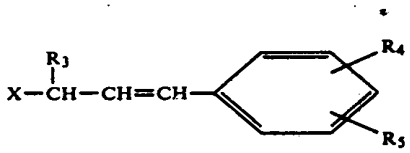
As used herein, the term "halogen" means fluorine, chlorine or bromine, preferably (unless otherwise indicated) fluorine or chlorine.

The invention also provides processes for the production of compounds of formula I, characterised by (a) reacting a compound of formula II,



II

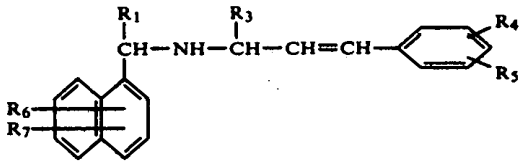
in which R_1, R_2, R_6 and R_7 are as defined above, with a compound of formula III,



III

in which R_3, R_4 and R_5 are as defined above and X is a leaving group,

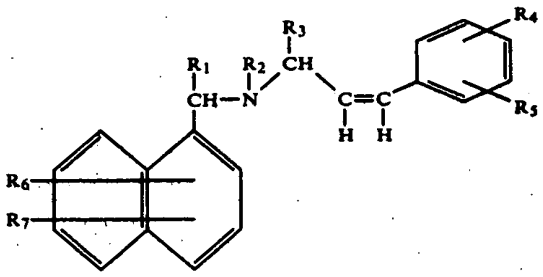
(b) introducing the group R_2 into a compound of formula IV,



IV

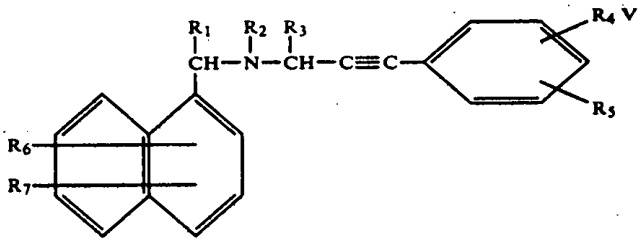
in which R_1, R_3, R_4, R_5, R_6 and R_7 are as defined above,

(c) producing a compound of formula Ia,



Ia

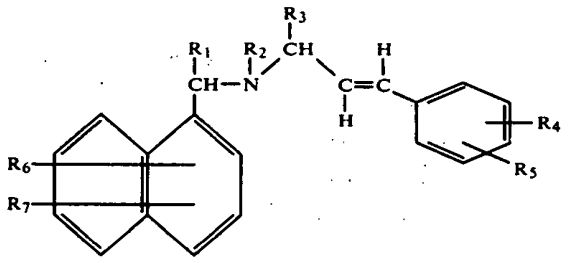
in which R_1 to R_7 are as defined above, by hydrogenating a compound of formula V,



V

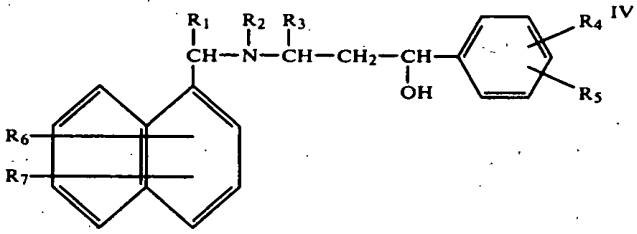
in which R_1 to R_7 are as defined above, or

(d) producing a compound of formula Ib,



Ib

in which R_1 to R_7 are as defined above, by splitting off water from a compound of formula VI,



IV

in which R_1 to R_7 are as defined above.

As indicated, process (c) leads to the products of the invention predominantly in cis isomeric form while process (d) leads to the products predominantly in trans isomeric form. The isomeric form of the products of processes (a) and (b) depends on the isomeric form of the starting material which can therefore be selected in accordance with desired form of the product.

Process (a) is suitably effected in an inert solvent, such as a lower alkanol, e.g. ethanol, optionally in aqueous admixture, an aromatic hydrocarbon, e.g. benzene or toluene, a cyclic ether, e.g. dioxane, or a carboxylic acid dialkylamide, e.g. dimethylformamide. The process may conveniently be carried out at a temperature of from room temperature to the boiling temperature of the reaction mixture, preferably at room temperature and is suitably effected in the presence of an acid binding agent, such as an alkali metal carbonate, e.g. sodium carbonate. The leaving group X in the compounds of formula III is suitably halogen, in particular chlorine or bromine, an organic sulphonyloxy group with 1 to 10 carbon atoms, e.g. C_{1-10}, preferably C_{1-4}, alkyl sulphonyloxy, in particular methylsulphonyloxy, or C_{1-3}-alkylphenylsulponyloxy, e.g. tosyloxy.

Process (b) may be effected in manner conventional for the "alkylation" (the term "alkylation" being used here to denote introduction of any of the hydrocarbyl groups R_2) of secondary amines, for example by direct "alkylation" with an "alkylating" agent, for example a halide or sulphate, or by reductive alkylation, in particular by reaction with an appropriate aldehyde and subsequent or simultaneous reduction. Reductive "alkylation" is suitably effected in an inert organic solvent, such as a lower alkanol, e.g. methanol, and at an elevated temperature, in particular at the boiling temperature of the reaction medium. The subsequent reduction may be effected with, for example, a complex metal hydride reducing agent, e.g. $NaBH_4$ or $LiAlH_4$. The reduction may also be effected simultaneously to the alkylation, for example by use of formic acid which may serve both as reducing agent and as a reaction medium.

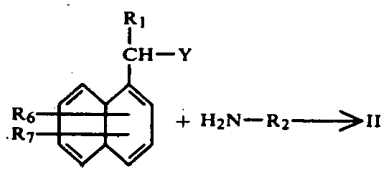
Process (c) is conveniently effected in an inert solvent, e.g. a lower alkanol, such as methanol or ethanol, a chlorinated hydrocarbon, e.g. methylene chloride, pyridine or an ester, such as ethylacetate. The hydrogenation may be carried out in conventional manner, for example employing a catalyst, such as palladium or platinum, suitably on a carrier such as Ba SO_4 or $CaCO_3$. The catalyst may also be partially inactivated, e.g. by pretreatment with lead salts (Lindlar catalysts).

Process (d) may suitably be carried out using a conventional dehydrating agent, e.g. an inorganic acid, such as hydrochloric acid or sulphuric acid, an organic acid, such as methane-, benzene- or p-toluenesulphonic acid, or anhydrides or halides thereof. The process may suitably be effected in an inert solvent although when an acid halide is employed as dehydrating agent, an excess thereof may be used to provide a reaction medium. An acid binding agent, e.g. a tertiary amine, such as trialkylamine or pyridine, is suitably present and the reaction temperature may, for example, range from $-10°$ to $+180°$ C. The process may also be effected using polyphosphoric acid. In this case, the reaction temperature is conveniently from 80° to 120° C. and an inert solvent, an inorganic acid, e.g. phosphoric acid or an organic acid, such as acetic acid, or an excess of the polyphosphoric acid, is suitably employed to provide a reaction medium.

The resulting compounds of formula I may be isolated and purified using conventional techniques. Where the process leads to mixtures of isomers, the individual isomers may be separated in conventional manner. Where required, free base forms thereof may be converted into acid addition salt forms in conventional manner, or vice versa.

The starting materials for use in the processes of the invention may, for example, be produced by the following reactions:

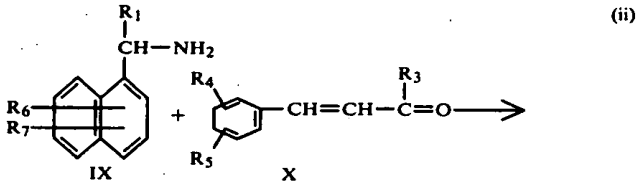
(i)



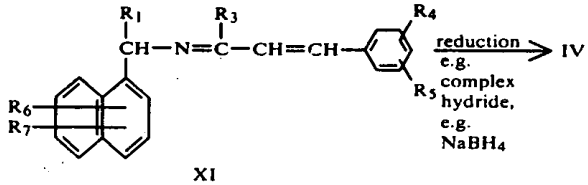
VII VIII

Y = halogen

(ii)

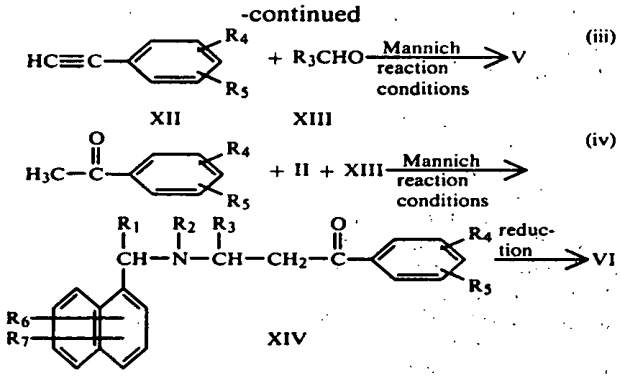


IX X



XI

-continued



R_1 to R_7 in the above formulae being as defined above.

These processes may be carried out in conventional manner.

The starting materials of formulae III, VII, VIII, IX, X, XII, XIII and XV are either known or may be produced in conventional manner from available materials.

The compounds of formula I are useful because they possess chemotherapeutic activity. In particular, they are useful as antimycotic agents, as indicated in vitro in various families and types of mycetes, including dermatophytes such as *T. rubrum, T. mentagrophytes, T. mentagrophytes var. quinckeanum, E. floccosum, M. canis, M. gypseum* and *M. racemosum, Aspergillus fumigatus, Microsporum canis, Sporotrychius schenkii, Candida albicans* and *Candida parapsilosis,* at concentrations of, for example 0.1 to 100 μg/ml, and in vivo in the experimental skin mycosis model in guinea pigs. In this model, guinea pigs are infected by sub-cutaneous application of e.g. *Trichophyton quinkeanum.* The test substance is administered once daily for 7 days beginning 24 hours after the infection either by local application by rubbing the test substance (taken up in polyethylene glycol) on the skin surface, or perorally or sub-cutaneously, the test substance being administered as a suspension. The activity is shown on local application at concentrations of for example 0.1 to 5%, in particular 0.1 to 0.5%. The oral activity is shown at dosages of, for example, 50 to 100 mg/kg.

For the above-mentioned use, the dose administered will of course vary depending on the compound employed, mode of administration and treatment desired. However, in general, satisfactory results are obtained when administered at a daily dosage of from 10 to 100 mg/kg of animal body weight, conveniently given in divided doses two to four times daily, or in sustained release form. For the larger mammals, the corresponding daily dosages are in the range of from 500 to 2000 mg, and dosage forms suitable for oral administration comprise from 125 to 1000 mg.

The compounds may be used in free base form or in the form of chemotherapeutically acceptable acid addition salts; suitable acids for salt formation include inorganic acids, such as hydrochloric acid, and organic acids, such as naphthalene-1,5-disulphonic acid and fumaric acid (particularly to form the hydrogen fumarate).

The compounds may be admixed with conventional chemotherapeutically acceptable diluents and carriers, and, optionally, other excipients and administered in such forms as tablets or capsules. The compounds may alternatively be administered topically in such conventional forms as ointments or creams. The concentration of the active substance in such topical application forms will of course vary depending on the compound employed, the treatment desired and the nature of the form etc. In general, however, satisfactory results are obtained at concentrations of from 0.05 to 5, in particular 0.1 to 1 wt. %.

The preferred compounds of the invention are in trans form. A compound with particularly interesting activity is the compound of Example 1, hereinafter.

The following Examples illustrate the invention. All temperatures are in °C.

EXAMPLE 1

Trans-N-(cinnamylmethyl)-N-methyl-(1-naphthylmethyl)amine [Process a)]

To a mixture of 1.42 g of methyl-(1-naphthylmethyl-)amine hydrochloride, 2.89 g of sodium carbonate and 10 ml of dimethyl formamide is added, at room temperature, 1.25 g of cinnamyl chloride, dropwise. After 18 hours stirring, at room temperature, the mixture is filtered and the filtrate is evaporated in vacuo. The residue is dissolved in toluene and, after drying over sodium sulphate, evaporated to obtain the heading compound, b.p. 162°–167° (0.015 Torr).

The free base may be converted, with isopropanolic hydrogen chloride solution, into the hydrochloride form, m.p. 177° C. (from propanol).

EXAMPLE 2

Trans-N-[3-(4-fluorophenyl)-2-propenyl]-N-methyl-(1-naphthylmethyl)amine [process b)]

(a) Trans-N-[3-(4-fluorophenyl)-2-propenyl]-(1-naphthylmethyl)amine

A mixture of 10 g of 1-aminomethylnaphthalene, 9.55 g of p-fluorocinnamaldehyde and 150 ml of benzene is heated in a reaction vessel equipped with a water separator, at reflux, until the theoretical amount of water has been separated. The mixture is cooled and evaporated to dryness. 5.78 g of the resulting Schiff's base in 60 ml of methanol, after warming to 50°, is mixed, with vigorous stirring, with 1.51 g of solid $NaBH_4$, portionwise, and the mixture is refluxed for 20 minutes. The resulting mixture may be used as such in the next stage. The title compound can be isolated as an oil, however, by evaporation and dividing the residue between aqueous $NaHCO_3$ solution and chloroform, drying the organic phase and evaporation.

(b) Trans-N-[3-(4-fluorophenyl)-2-propenyl]-N-methyl-(1-naphthylmethyl)amine [process b)]

(i) The reaction mixture resulting from step (a) is refluxed, after addition of 16 ml of 37% aqueous formaldehyde solution, for 1½ hours. The mixture is cooled and mixed, portionwise, in an ice bath and with vigorous stirring, with 7.6 g of $NaBH_4$. After 4 hours, the residue is centrifugally divided between aqueous $NaHCO_3$ solution and chloroform. The organic phase is dried and centrifuged to obtain the heading compound as an oil, m.p. hydrochloride form: 191°–206°.

(ii) The oil resulting from step (a) (2.9 g) is refluxed with 3.3 g of formic acid (98–100%) and 0.81 ml of 37% aqueous formaldehyde mixture is evaporated in vacuo, and the residue divided between chloroform and aqueous $NaHCO_3$ solution. The aqueous phase is washed with brine, dried and evaporated to obtain the heading compound, m.p. hydrochloride form: 191°–206°.

EXAMPLE 3

Cis-N-[3-(4-chlorophenyl)-2-propenyl]-N-methyl-1-naphthylmethyl)amine [process c)]

(a) N-[3-(4-Chlorophenyl)propargyl]-N-methyl-(1-naphthylmethyl)amine

15 g of methyl-(1-naphthylmethyl)amine, 12 g of p-chlorophenylacetylene, 2.61 g of paraformaldehyde and 1.1 g of zinc chloride are refluxed in absolute dioxane, in the absence of water, for 3 hours. The mixture is then evaporated and the residue is divided between saturated aqueous $NaHCO_3$ solution and chloroform. The organic phase is dried and evaporated and the crude product is recrystallised from ethanol, m.p. 74°–75°.

(b) Cis-N-[3-(4-chlorophenyl)-2-propenyl]-N-methyl-(1-naphthylmethyl)amine

3 g of [3-(4-chlorophenyl)propargyl]-methyl-(1-naphthylmethyl)amine are dissolved in 50 ml of absolute pyridine. The solution is hydrogenated employing 150 mg of $Pd/BaSO_4$ (5%) until the theoretical amount of hydrogen has been taken up. The catalyst is filtered off and the mixture evaporated. The oily residue is chromatographed over silica gel using benzene/ethyl acetate (9:1) as eluant, to obtain the pure heading compound, m.p. 41°–42° (from ethanol/water).

EXAMPLE 4

Trans-N-methyl-N-[3-(4-tolyl)-2-propenyl]-(1-naphthylmethyl)amine

(a) N-Methyl-(1-naphthylmethyl)amine

17.6 g of 1-chloromethyl-naphthalene in 40 ml of absolute ethanol is added, dropwise, at 0° to 5°, to 100 ml of a 33% solution of methylamine in absolute ethanol. The mixture is allowed to stand overnight and is then evaporated. The residue is taken up in a little chloroform and washed with 100 ml of 1 N sodium hydroxide solution and with water. The organic phase is dried and evaporated to dryness. The residue is distilled at 0.01 Torr to obtain the heading compound as main fraction, b.p. 85°–87°.

(b) β-(N-methyl-(1-naphthylmethyl)amino]ethyl-(4-tolyl)ketone

17.1 g of methyl-(1-naphthylmethyl)amine are dissolved in 200 ml of methanol and 10 ml of concentrated hydrochloric acid, 13.4 g of 4-tolylmethylketone and 100 ml of 35% formaldehyde solution are sequentially added. The mixture is refluxed for 1½ hours, with stirring, cooled, diluted with 1 liter of water, made alkaline with 30% sodium hydroxide solution and exhaustively extracted with chloroform. The organic extract is dried and evaporated to dryness and the oily residue is dissolved in petroleum ether and allowed to crystallise in the cold, to obtain the heading compound, m.p. 92°–95°.

(c) 3-[N-methyl]-(1-naphthylmethyl)amino]-1-(4-tolyl)-propan-1-ol

To a solution of 7.5 g of β-[methyl-(1-naphthylmethyl)amino]ethyl-(4-tolyl)ketone in 400 ml of methanol is added, portionwise, at room temperature, 1 g of $NaBH_4$. The mixture is stirred for 15 minutes and the solvent is then evaporated off. The oily residue is taken up in chloroform and washed with water. The organic phase is dried and evaporated to dryness to obtain the crude heading product which is used as such in the next stage.

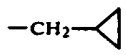
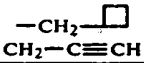
(d) Trans-N-methyl-N-[3-(4-tolyl)-2-propenyl]-(1-naphthylmethyl)-amine

8.4 g of 3-[methyl]-(1-naphthylmethyl)amino]-1-(4-tolyl)-propan-1-ol are refluxed, with stirring, in 300 ml of 5 N hydrochloric acid for 1½ hours. The mixture is isolated by addition of ice, made alkaline with 30% sodium hydroxide solution and exhaustively extracted with chloroform. The chloroform extract is dried over sodium sulphate, filtered and evaporated to dryness. The oily residue is dissolved in absolute ethanol and made acid with etheric hydrochloric acid. After addition of ether, the heading compound is obtained, m.p. 207°–211°.

In manner analogous to the Example indicated, and employing appropriate starting materials in approximately equivalent amounts, the compounds of formula I indicated in the following Table may be obtained.

Ex.	R_1	R_2	R_3	R_4	R_5	R_6	R_7	Analogous to Example	M.P. °C.	Centrifugation
5	H	CH_3	H	4-Cl	H	H	H	1, 2 or 4	209–212[1]	Trans
6	H	CH_3	H	4-CH_3	H	H	H	1 or 2	207–211[1]	"
7	H	CH_3	H	4-F	H	H	H	1 or 4	191–206[1]	"
8	H	CH_3	H	4-Cl	3-Cl	H	H	1, 2 or 4	187–192[1]	"
9	H	CH_3	H	4-OCH_3	H	H	H	1, 2 or 4	193–196[1]	"
10	H	CH_3	H	H	H	2-OH	H	1, 2 or 4	197–199[2]	"
11	H	$CH(CH_3)_2$	H	H	H	H	H	1, 2 or 4	225–230[2]	"
12	H	CH_3	H	H	H	2-CH_3	H	1, 2 or 4	204–208[1]	"
13	CH_3	CH_3	H	H	H	H	H	1, 2 or 4	213–215[2]	"
14	H	CH_3	H	2-F	H	H	H	1, 2 or 4	176–181[1]	"
15	H	CH_3	H	2-Cl	H	H	H	1, 2 or 4	178–181[1]	"
16	H	CH_3	H	4-OH	H	H	H	1, 2 or 4	196–200[2]	"
17	H	C_2H_5	H	H	H	H	H	1, 2 or 4	127–129[3]	"
18	H	CH_3	H	H	H	4-Cl	H	1, 2 or 4	198–208[1]	"
19	H	CH_3	H	H	H	4-CH_3	H	1, 2 or 4	197–201[1]	"
20	H	CH_3	H	H	H	2-OCH_3	H	1, 2 or 4	248–250[2]	"
21	H	CH_3	H	H	H	4-OCH_3	H	1, 2 or 4	211–214[1]	"
22	H	CH_3	H	H	H	H	H	1, 2 or 3	oil[4,5]	cis
23	H	CH_3	H	4-F	H	H	H	1, 2 or 3	oil[6,7]	"
24	H	CH_3	H	4-Cl	H	H	H	1 or 2	41–42	"
25	H	CH_2—CH=CH_2	H	H	H	H	H	1, 2 or 4	95–103[1]	trans
26	H	CH_3	H	H	H	H	H	2 or 4	177–179[1]	"
27	H		CH_3	H	H	4-Cl	H	1, 2 or 4		"

-continued

Ex.	R_1	R_2	R_3	R_4	R_5	R_6	R_7	Analogous to Example	M.P. °C.	Centrifugation
28	H		H	H	H	4-Cl	6-Cl	1, 2 or 4		"
29	CH_3		H	H	4-Cl	4-Cl	H	1, 2 or 3		cis
30	H		H	H	H	4-CF_3	H	1, 2 or 4		trans
31		$CH_2-C\equiv CH$	H	4-NO_2	H	H	H	1, 2 or 3		cis

Key to Table

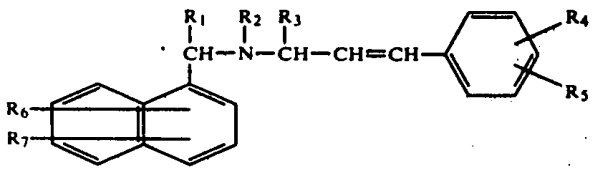
1. Hydrochloride form
2. Naphthalen-1,5-disulphonate form
3. Hydrogen fumarate form

NMR ($CDCl_3$/RT/TMS): $\delta=8.3$ (m,1H), $\delta=7.2$–8.0 (m,11H), $\delta=6.60$ (m,1H), $\delta=5.90$ (m,1H), $\delta=3.90$ (s,2H), $\delta=3.35$ (m,2H), $\delta=2.25$ (s,3H) [s=singlet, m=multiplet]

5. Starting material VI for process (c); m.p. hydrochloride form 140°–142° (from propanol/ether)
6. NMR ($CDCl_3$/RT/TMS): $\delta=8.3$ (m,1H), $\delta=6.8$–7.9 (m,10H) $\delta=6.55$ (m,1H), $\delta=5.90$ (m,1H), $\delta=3.90$ (s,2H), $\delta=3.3$ (m,2H), $\delta=2.25$ (s,3H) [s=singlet, m=multiplet]
7. Starting material VI for process (c); m.p. 69°–70° (from ethanol).

What is claimed is:

1. Compounds of formula I,



I

in which

R_1 is hydrogen or alkyl,

R_2 is alkyl, alkenyl, alkynyl, cycloalkyl or cycloalkylalkyl,

R_3 is hydrogen or lower alkyl, and

R_4, R_5, R_6 and R_7, which may be the same or different, each signifies hydrogen, halogen, trifluoromethyl, hydroxy, nitro or lower alkyl or alkoxy, and

chemotherapeutically acceptable acid addition salts thereof.

2. A chemotherapeutic composition comprising a chemotherapeutic effect amount of a compound of claim 1 in association with a chemotherapeutically acceptable diluent or carrier.

3. A method of treating mycotic disorders comprising administering to an animal in need of such treatment, an effective amount of a compound of claim 1.

4. A compound according to claim 1 in which R_2 is alkyl of 1 to 6 carbon atoms.

5. A compound according to claim 4 in which R_1 is hydrogen and R_3 is hydrogen.

6. The compound of claim 1 which is Trans-N-(cinnamyl)-N-methyl-(1-naphthylmethyl)amine.

7. The compound of claim 1 which is Trans-N-[3-(4-fluorophenyl)-2-propenyl]-N-methyl-(1-naphthylmethyl)amine.

8. The compound of claim 1 which is Cis-N-[3-(4-chlorophenyl)-2-propenyl]-N-methyl-1-naphthylmethyl)amine.

9. The compound of claim 1 which is Trans-N-methyl-N-[3-(4-tolyl)-propenyl]-(1-naphthylmethyl)amine.

10. The compound of claim 1 in Trans form in which R_1, R_2, R_3, R_4, R_5, R_6 and R_7 are H, CH_3, H, 4-Cl, H, H and H, respectively.

11. The compound of claim 1 in Trans form in which R_1, R_2, R_3, R_4, R_5, R_6 and R_7 are H, CH_3, H, 4-Cl, 3-Cl, H and H, respectively.

12. The compound of claim 1 in Trans form in which R_1, R_2, R_3, R_4, R_5, R_6 and R_7 are H, CH_3, H, 4-OCH_3, H, H and H, respectively.

13. The compound of claim 1 in Trans form in which R_1, R_2, R_3, R_4, R_5, R_6 and R_7 are H, CH_3, H, H, H, 2-OH and H, respectively.

14. The compound of claim 1 in Trans form in which R_1, R_2, R_3, R_4, R_5, R_6 and R_7 are H, $CH(CH_3)_2$, H, H, H, H and H, respectively.

15. The compound of claim 1 in Trans form in which R_1, R_2, R_3, R_4, R_5, R_6 and R_7 are H, CH_3, H, H, H, 2-CH_3 and H, respectively.

16. The compound of claim 1 in Trans form in which R_1, R_2, R_3, R_4, R_5, R_6 and R_7 are CH_3, CH_3, H, H, H, H and H, respectively.

17. The compound of claim 1 in Trans form in which R_1, R_2, R_3, R_4, R_5, R_6 and R_7 are H, CH_3, H, 2-F, H, H and H, respectively.

18. The compound of claim 1 in Trans form in which R_1, R_2, R_3, R_4, R_5, R_6 and R_7 are H, CH_3, H, 2—Cl, H, H and H, respectively.

19. The compound of claim 1 in Trans form in which R_1, R_2, R_3, R_4, R_5, R_6 and R_7 are H, CH_3, H, 4—OH, H, H and H, respectively.

20. The compound of claim 1 in Trans form in which R_1, R_2, R_3, R_4, R_5, R_6 and R_7 are H, C_2H_5, H, H, H, H and H, respectively.

21. The compound of claim 1 in Trans form in which R_1, R_2, R_3, R_4, R_5, R_6 and R_7 are H, CH_3, H, H, H, 4—Cl and H, respectively.

22. The compound of claim 1 in Trans form in which R_1, R_2, R_3, R_4, R_5, R_6 and R_7 are H, CH_3, H, H, H, 4—CH_3 and H, respectively.

23. The compound of claim 1 in Trans form in which R_1, R_2, R_3, R_4, R_5, R_6 and R_7 are H, CH_3, H, H, H, 2—OCH_3 and H, respectively.

24. The compound of claim 1 in Trans form in which R_1, R_2, R_3, R_4, R_5, R_6 and R_7 are H, CH_3, H, H, H, 4—OCH_3 and H, respectively.

25. The compound of claim 1 in Cis form in which R_1, R_2, R_3, R_4, R_5, R_6 and R_7 are H, CH_3, H, H, H, H and H, respectively.

26. The compound of claim 1 in Cis form in which R_1, R_2, R_3, R_4, R_5, R_6 and R_7 are H, CH_3, H, 4-F, H, H and H, respectively.

27. The compound of claim 1 in Trans form in which R_1, R_2, R_3, R_4, R_5, R_6 and R_7 are H, $CH_2—CH=CH_2$, H, H, H, H and H, respectively.

28. A pharmaceutical composition according to claim 2 in which the compound is Trans-N-cinnamyl-N-methyl(1-naphthylmethyl)amine.

29. A method according to claim 3 in which the compound is Trans-N-cinnamyl-N-methyl-(1-naphthylmethyl)amine.

* * * * *

APPENDIX B - PART I

Naftifine Hydrochloride Cream 1%
Chronology of Significant Regulatory Activities

January 17, 1980	Dorsey Laboratories, a division of Sandoz, Inc., files IND #17-148 for naftifine hydrochloride.
March 6, 1980	Preclinical Report entitled, "An Investigation of the Local Sensitising Effect of Intracutaneous Administration to Albino Guinea Pigs" sent to FDA.
June 30, 1980	Preclinical Reports entitled, "Investigation of Cardiovascular Effects of SM 105-843 in Anesthetized Dogs" and "Mutagenicity Evaluation Using Salmonella Typhimurin" sent to FDA.
July 18, 1980	Preclinical Reports entitled, "Investigation of Cardiovascular Effects of SM 105-843 in Anesthetized Dogs", "Mutagenicity Evaluation Using Salmonella Typhimurin" and "Investigation of Cardiovascular Effects of SM 105-843, Given by Intravenous Infusion In Anesthetized Cats" sent to FDA.
November 26, 1980	Study start-up documents for Multi-Centers No. 3 and 4 entitled, "The Antifungal Efficacy and Safety of SM 105-843 vs. Commercially Available Lotrimin Cream and Placebo" sent to FDA.
December 8, 1980	FDA was advised that an additional investigator added to Study 3.
March 6, 1981	Amendment to protocol for one investigator participating in Studies 3 and 4 to provide for the open-label continuation of those patients who have responded well, and Amendment to protocol for Studies 3 and 4 to include patients with candida albicans by various investigators sent to the FDA.

March 26, 1981	FDA was advised that an additional investigator added to Study 3, and An amendment to protocol for one investigator in Study 4 is to include patients with candida albicans.
April 1, 1983	Letter from FDA requesting Annual Progress Report.
July 13, 1983	Progress Report for period January 1980 to July 1, 1983 sent to FDA including information concerning -Study No. 1, conducted May 5, 1980-July 7, 1980 -Study No. 2, conducted May 7, 1980-June 23, 1980 -Studies No. 3 and 4, conducted December, 1980-October, 1981 (multicenter studies)
July 22, 1983	Sandoz assumes responsibilities for IND.
August 5, 1983	FDA was informed that Sandoz is granting cross reference rights to Allergan.
April 3, 1985	FDA letter requests progress report.
April 29, 1986	Sandoz discontinues IND noting that Allergan developed the compound under cross reference to our IND and has referenced same in their own original NDAs for naftifine hydrcholoride.
May 16, 1986	FDA acknowledges discontinuance of the IND.

APPENDIX B - PART 2

In respect to the filing for
Naftin® (naftifine hydrochloride) Cream 1%
NDA 19-599
by
HERBERT LABORATORIES

Chronology of Significant Regulatory Activities

10/07/83	Submission to FDA	Original IND filed
10/18/83	Letter from FDA	Acknowledgement of receipt (10/11/83) of IND 22,919
11/07/83	Request from FDA	Request (by telephone) for manufacturing controls information on clinical test articles
11/10/83	Submission to FDA	Response to 11/07/83 request for manufacturing controls information
11/21/83	Letter from FDA	Request for manufacturing controls information on clinical test articles
11/21/83	Letter from FDA	Request for clinical protocol and investigator's brochure (information actually already on file)
01/17/84	Submission to FDA	Reply to FDA letter of 11/21/83 on clinical protocols
01/20/84	Submission to FDA	Answer to FDA letter of 11/21/83 on formulations
10/08/84	Submission to FDA	Clinical protocol and amendments
10/17/84	Submission to FDA	Submission of drug experience report
11/20/84	Submission to FDA	IND Progress Report (10/84)
11/27/84	Submission to FDA	Submission of drug experience report
02/21/85	Submission to FDA	Submission of drug experience report
07/10/85	Submission to FDA	Submission of chemistry information on naftifine structure
12/05/85	Submission to FDA	IND Progress Report (11/85)

02/10/86	Letter to FDA	Questions on suitability of specific clinical studies to support the proposed indications, to be discussed at a 03/04/86 meeting
03/04/86	Submission to FDA	Submission of drug experience report
03/14/86	Submission to FDA	Original NDA filed
03/21/86	Letter from FDA	Acknowledgement of receipt (03/18/86) of NDA
06/05/86	Request from FDA	Request (by telephone) for raw material specification sheet
06/12/86	Submission to FDA	Response to 06/05/86 request for raw material specification sheet
08/06/86	Request from FDA	Request (by telephone) for clarification/explanation of stability concerns
08/06/86	Submission to FDA	Response to 08/06/86 request on stability concerns
11/24/86	Submission to FDA	IND Progress Report (10/86)
03/20/87	Submission to FDA	Updated stability and methods validation
05/07/87	Letter from FDA	Formal response to submission (received 03/24/87) of updated stability report, with an extension by FDA of their review period to 06/24/87
06/23/87	Submission to FDA	Commitment to include a homogeneity specification for the finished product
07/01/87	Submission to FDA	Methods validation materials
09/10/87	Submission to FDA	Submission of additional copies of draft labeling to the Consumer Safety Officer, at his request
09/17/87	Submission to FDA	Methods validation materials sent to FDA Los Angeles laboratory, to verify assay methods
09/21/87	Submission to FDA	Submission of raw material standard to FDA Los Angeles laboratory

10/22/87	Submission to FDA	IND Progress Report (10/87)
12/22/87	Letter from FDA	Approvable letter with suggestions for revised product indications and labeling
01/04/88	Submission to FDA	Request for meeting with FDA to discuss approvable letter of 12/22/87
02/05/88	Submission to FDA	Formal response to approvable letter of 12/22/87 with revised draft labeling
02/23/88	Request from FDA	Request (by telephone) for a further minor modification to labeling
02/23/88	Submission to FDA	Response to 02/23/88 request for revised labeling
02/29/88	Letter from FDA	NDA approved

APPENDIX C

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re: U.S. Patent No. 4,282,251 :

Issued: August 4, 1981 :

To: Daniel Berney :

For: TRANS-N-CINNAMYL-N-METHYL-(1-NAPHTHYLMETHYL)AMINE :

Honorable Commissioner of
Patents and Trademarks
Washington, D.C. 20231

DECLARATION

Sir:

The undersigned attorney for Sandoz Pharmaceuticals Corporation, which is the Applicant for Extension of Patent Term under 35 USC 156 respecting U.S. Patent 4,282,251, hereby declares as follows:

(1) That he is a patent attorney authorized to practice before the Patent and Trademark Office and has general authority from Sandoz Pharmaceuticals Corporation to act on behalf of such corporation in patent matters;

(2) That he has reviewed and understands the contents of the application being submitted herewith pursuant to 35 USC 156 and the Patent and Trademark Office's Rules on Patent Term Extension in 37 CFR §1.710 through §1.785;

(3) That he believes U.S. Patent 4,282,251 is subject to extension pursuant to §1.710 of said Rules on Patent Term Extension;

(4) That he believes an extension of the length claimed is fully justified under 35 USC 156 and the applicable regulations; and

(5) That he believes the patent for which the extension is being sought meets the conditions for extension of the term of a patent as set forth in §1.720 of said Rules on Patent Term Extension.

The undersigned hereby declares further that all statements made herein of his own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under section 1001 of Title 18 of the United States code and that such willful false statements may jeopardize the validity of the application or any extension of patent term issuing thereon.

Further declarant sayeth not.

Signed this 25th day April, 1988.

Gerald D. Sharkin
Vice President
Patent and Trademark Affairs

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GDS/vls